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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/616,284

07/14/2000

Larry Gold

NEX77/CIP2

6509

25871 7590 06/05/2002
SWANSON & BRATSCHUN L.L.C.
1745 SHEA CENTER DRIVE
SUITE 330
HIGHLANDS RANCH, CO 80129

EXAMINER

FORMAN, BETTY J

ART UNIT	PAPER NUMBER
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1634

#16

DATE MAILED: 06/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/616,284	GOLD ET AL.
	Examiner	Art Unit
	BJ Forman	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 26 February 2002.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 18 and 19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 18 and 19 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>9,15</u> .	6) <input checked="" type="checkbox"/> Other: <u>Raw Sequence Listing Error</u> <u>Notice to Comply</u> _____

FINAL ACTION

1. This action is in response to papers filed 26 February 2002 in Paper No. 12 in which claim 18 was amended, and claims 1-17 were canceled. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 8 dated 15 August 2001 under 35 U.S.C. 103(a) are maintained. All of the arguments have been thoroughly reviewed and are discussed below.

Currently claims 18 and 19 are under prosecution.

Priority

reiterated from the previous Office Action

2. The instant application claims priority as a CIP to co-pending application 09/356,233 filed 07/16/1999, which is a CIP of 09/232,946 filed 01/19/1999, which is a CIP of 08/792,075 filed 01/31/1997 and a CIP of 09/143,190 filed 08/27/1998, which is a CON of 08/469,609 filed 06/06/1995, which is a CON of 07/714,131 filed 01/10/1991, which is a CIP of 07/536,428 filed 06/11/1990. Instant Claims 18 and 19 are drawn to a method for identifying a nucleic acid ligand that photocrosslinks to a protein from a candidate mixture of nucleic acids wherein each member of said candidate mixture contains a photoreactive group and wherein the method steps are performed at one or more work stations by a cartesian robotic manipulator controlled by a computer. The instantly claimed photocrosslinking and computer controlled robotic manipulator are limitations which were not disclosed in the '075, '190, '609, '131, or '428 applications. Therefore, the effective filing date for instant Claims 18 and 19 is the filing date of the '946 application i.e. 19 January 1999.

Claim Objections

3. The previous objection to Claim 18 is withdrawn in view of the amendments.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al (Biotechnology. Prog. 1998, 14:845-850) in view of Hanna (Methods in Enzymology, 1989, 180: 383-405).

Regarding Claim 18, Cox et al. teach a method for identifying a nucleic acid ligand from a candidate mixture wherein the ligand interacts with a target (Abstract lines 1-4 and page 845, left column, second paragraph, lines 1-5) the method comprising: contacting the candidate mixture with the target (page 846-847, "Selection Regime"); partitioning the nucleic acid-target complexes (page 847, left column, lines 1-19); and identifying the nucleic acid ligand (page 847, right column, first full paragraph) and wherein method steps are performed at one or more work stations on a work surface by a Cartesian robotic manipulator i.e. manipulate liquids in an x-y-z axis (page 847, right column, second full paragraph) controlled by a computer (page 845, right column, last 3 lines and page 846, left column, lines 1-11). Cox et al. do not teach the nucleic acid ligand contains a photoreactive group and irradiating the nucleic acid-target complex to photocrosslink the nucleic acid-protein. However, modifying

a nucleic acid with a photoreactive group and irradiating to thereby photocrosslink modified nucleic acid-protein complexes was well known in the art at the time the claimed invention was made as taught by Hanna. Specifically, Hanna teaches a method for identifying a nucleic acid that photocrosslinks to a protein comprising: contacting a candidate mixture of nucleic acids with a protein; irradiating to photocrosslink nucleic acid-protein complexes; partitioning the photocrosslinked nucleic acid-protein complexes (page 405, last paragraph-page 406, fifth full paragraph, *Isolation and Analysis*); and identifying a nucleic acid photocrosslinked to the protein (page 408, last paragraph-through page 409). Additionally, Hanna teaches that modification of an RNA with photoreactive groups allows for the study of RNA-protein interactions in their native conformations (page 389, third full paragraph, lines 1-3) and that RNA-protein photocrosslinking traps weak or transient RNA-protein interactions which, if not photocrosslinked, might not survive isolation (page 383, lines 7-10). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify nucleic acid-protein complex partitioning taught by Cox et al. by modifying the nucleic acid with photoreactive groups and irradiating nucleic acid-protein complexes to photocrosslink the complexes prior to partitioning to thereby obtain nucleic acid-protein complexes in their native conformation and obtain weak or transient nucleic acid-protein interactions as taught by Hanna (page 383, lines 7-10 and page 389, third full paragraph, lines 1-3) for the expected benefit of obtaining otherwise unobtainable complexes.

Regarding Claim 19, Cox et al. teach a method for identifying a nucleic acid ligand from a candidate mixture wherein the ligand interacts with a target as defined by Gold et al. (Abstract lines 1-4 and page 845, left column, second paragraph, lines 1-5) the method comprising: contacting the candidate mixture with the target (page 846-847, "Selection Regime"); partitioning the nucleic acid-target complexes (page 847, left column, lines 1-19); amplifying the increased affinity nucleic acids to yield a ligand-enriched mixture of nucleic acids (page 847, left column, second full paragraph) and identifying the nucleic acid ligand

(page 847, right column, first full paragraph) and wherein method steps are performed at one or more work stations on a work surface by a Cartesian robotic manipulator i.e. manipulate liquids in an x-y-z axis (page 847, right column, second full paragraph) controlled by a computer (page 845, right column, last 3 lines and page 846, left column, lines 1-11). Cox et al. do not teach the nucleic acid ligand contains a photoreactive group and irradiating the nucleic acid-target complex to photocrosslink the nucleic acid-protein. However, modifying a nucleic acid with a photoreactive group and irradiating to thereby photocrosslink modified nucleic acid-protein complexes was well known in the art at the time the claimed invention was made as taught by Hanna. Specifically, Hanna teaches a method for identifying a nucleic acid that photocrosslinks to a protein comprising: contacting a candidate mixture of nucleic acids with a protein; irradiating to photocrosslink nucleic acid-protein complexes; partitioning the photocrosslinked nucleic acid-protein complexes (page 405, last paragraph-page 406, fifth full paragraph, Isolation and Analysis); and identifying a nucleic acid photocrosslinked to the protein (page 408, last paragraph-through page 409). Additionally, Hanna teaches that modification of an RNA with photoreactive groups allows for the study of RNA-protein interactions in their native conformations (page 389, third full paragraph, lines 1-3) and that RNA-protein photocrosslinking traps weak or transient RNA-protein interactions which, if not photocrosslinked, might not survive isolation (page 383, lines 7-10). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify nucleic acid-protein complex partitioning taught by Cox et al. by modifying the nucleic acid with photoreactive groups and irradiating nucleic acid-protein complexes to photocrosslink the complexes prior to partitioning to thereby obtain nucleic acid-protein complexes in their native conformation and obtain weak or transient nucleic acid-protein interactions as taught by Hanna (page 383, lines 7-10 and page 389, third full paragraph, lines 1-3) for the expected benefit of obtaining otherwise unobtainable complexes.

Response to Arguments

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6. Applicant argues that Cox et al do not describe a SELEX-like or aptamer selection process but instead generally refer to selection of nucleic acid aptamers. Applicant further argues that Cox et al do not attempt to automate aptamer selection, but at most provide an invitation to experiment with automation of a selection method to obtain nucleic acid aptamers to protein. Therefore, Applicant argues, Cox et al is far too speculative to reasonably predict the success of automation of a SELEX-like method. The arguments have been considered but are not found persuasive because Cox et al specifically teach their automated selection method is useful for generating "nucleic acid aptamers in days rather than months" (Abstract). Additionally, the arguments are not found persuasive because Applicant does not provide evidence supported by an appropriate affidavit or declaration regarding inoperability of the Cox et al teaching.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. (see MPEP § 706.01(c)).

Applicant argues that Cox et al do not teach adding the step of irradiating oligonucleotides containing photoreactive groups to form crosslinked aptamer-target complexes and there is no apparatus in Cox et al for irradiating. Applicant further argues that use of oligonucleotides with photoreactive groups, the mixing and complexing of such oligonucleotides with protein targets and the irradiation of the complexes introduces more steps and variables into the automation process which introduces more unpredictability. Applicant argues that Hanna does not cure the deficiencies of Cox et al because Hanna is not concerned with screening of millions of synthetic oligonucleotides to identify nucleic acid ligands and makes no reference to a SELEX-like process. In response to applicant's arguments against the Cox et al and Hanna references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that there is insufficient suggestion in Hanna and Cox et al to support a case of *prima facie* obviousness, but at most provide only general guidance and therefore only an invitation to experiment. The argument has been considered but is not found persuasive because Hanna clearly teach their photocrosslinking is useful for analyzing RNA-protein complexes and they teach motivation to photocrosslink such complexes i.e. modification of an RNA with photoreactive groups allows for the study of RNA-protein

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interactions in their native conformations (page 389, third full paragraph, lines 1-3) and that RNA-protein photocrosslinking traps weak or transient RNA-protein interactions which, if not photocrosslinked, might not survive isolation (page 383, lines 7-10). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify nucleic acid-protein complex partitioning taught by Cox et al. by modifying the nucleic acid with photoreactive groups and irradiating nucleic acid-protein complexes to photocrosslink the complexes prior to partitioning to thereby obtain nucleic acid-protein complexes in their native conformation and obtain weak or transient nucleic acid-protein interactions as taught by Hanna (page 383, lines 7-10 and page 389, third full paragraph, lines 1-3) for the expected benefit of obtaining otherwise unobtainable complexes.

Applicant argues that there is no suggestion in the teaching of Cox et al and Hanna to combine their teaching; there is not teaching in Hanna that photocrosslinking could be useful in screening millions of nucleic acids or automated screening; and there is no teaching in Cox et al that photocrosslinking could be incorporated into an automated nucleic acid selection process and as such *prima facie* obviousness has not been established. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Cox et al teach an automated method of nucleic acid ligand selection and Hanna teaches photocrosslinking of RNA-protein complexes wherein the crosslinking permits study of RNA-protein interactions in their native conformations (page 389, third full paragraph, lines 1-3) and that RNA-protein photocrosslinking traps weak or transient RNA-protein interactions which, if not photocrosslinked, might not survive isolation (page 383, lines 7-10). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify nucleic acid-protein complex partitioning taught by Cox et al. by modifying the nucleic acid with photoreactive groups and irradiating nucleic acid-protein complexes to photocrosslink the complexes prior to partitioning to thereby obtain nucleic acid-protein complexes in their native conformation and obtain weak or transient nucleic acid-protein interactions as taught by Hanna (page 383, lines 7-10 and page 389, third full paragraph, lines 1-3) for the expected benefit of obtaining otherwise unobtainable complexes.

Applicant argues that the motivation provided by the examiner is not the necessary motivation because the purpose of the instant invention is to obtain aptamers with greater

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affinity not those with weak or non-specific binding. In response to applicant's argument that the instant invention is not drawn to obtaining weak or non-specific binding aptamers, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues unexpected results have been obtained using the automated partitioning step of photoSELEX and cites co-pending Application 09/993,294 as evidence. However, Applicant has not illustrated how or why the results obtained in the '294 application are unexpected. Therefore, the argument is not found persuasive because it is not supported by evidence.

7. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al. (U.S. Patent No. 5,475,096, filed 10 June 1991) in view of Cathcart et al. (U.S. Patent No. 5,443,791, filed 7 August 1992) and Hanna (Methods in Enzymology, 1989, 180: 383-405).

Regarding Claim 18, Gold et al. teach a method for the identification of a nucleic acid ligand from a candidate mixture of nucleic acids (Column 9, lines 14-40, Fig. 2 and Example 1), wherein said nucleic acid ligand binds a protein (Column 13, lines 1-6 and 15-20) the method comprising: contacting the candidate mixture with the protein wherein the nucleic acids having an increased affinity to the protein relative to the candidate mixture to form complexes (Column 36, Example 1, Column 36, lines 58-62); partitioning the increased affinity nucleic acids from the remainder of the candidate mixture (Column 13, lines 21-35 and Example 1, Column 36, lines 58-62); and identifying the nucleic acid ligand (Example 1, Column 37, lines 24-28). Gold et al. do not teach the method is automated wherein method steps are performed at one or more work stations on a work surface by a Cartesian robotic manipulator controlled by a computer. However, automated methods of identifying a nucleic acid from a mixture of nucleic acids were known in the art as taught by Cathcart et al. Specifically, Cathcart et al. teach the method for automated identification of a nucleic acid

binding partner from a mixture of nucleic acids using a Cartesian robotic for contacting a nucleic acid binding partner within a mixture of nucleic acids (Fig. 1, #11, Column 13, lines 52-61 and Column 26, lines 20-38); a means for partitioning of nucleic acids having a high affinity for the nucleic acid binding partner using particle-bound affinity pairs (Fig. 1, #26 or 29 and Column 14, lines 9-68); and an identification means for identifying nucleic acid binding partner (Column 26, lines 20-23, Column 27, lines 64-68 and Column 28, lines 1-10). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply automated machine of Cathcart et al. wherein nucleic acid binding partners are identified to the closely related method of Gold et al. wherein nucleic acid ligands are identified because the skilled practitioner would have known that nucleic acid ligands and nucleic acid binding partners would have the same physical and chemical properties and because one skilled in the art would have known that automated methods produce consistent experimental results, precise manipulations and reduce hands-one operator time as taught by Cathcart et al. (Column 29, lines 50-55) therefore one skilled in the art would have been motivated to apply the automation of Cathcart et al. to the method of Gold et al. for the expected benefits of economy of time and labor. Gold et al. does not teach the nucleic acid ligand contains a photoreactive group and irradiating the nucleic acid-target complex to thereby photocrosslink the nucleic acid-protein complex. However, modifying a nucleic acid with a photoreactive group and irradiating to thereby photocrosslink modified nucleic acid-protein complexes was well known in the art at the time the claimed invention was made as taught by Hanna. Specifically, Hanna teaches a method for identifying a nucleic acid that photocrosslinks to a protein comprising: contacting a candidate mixture of nucleic acids with a protein; irradiating to photocrosslink nucleic acid-protein complexes; partitioning the photocrosslinked nucleic acid-protein complexes (page 405, last paragraph-page 406, fifth full paragraph, Isolation and Analysis); and identifying a nucleic acid photocrosslinked to the protein (page 408, last paragraph-through page 409). Additionally, Hanna teaches that modification of an RNA with

photoreactive groups allows for the study of RNA-protein interactions in their native conformations (page 389, third full paragraph, lines 1-3) and that RNA-protein photocrosslinking traps weak or transient RNA-protein interactions which, if not photocrosslinked, might not survive isolation (page 383, lines 7-10). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify nucleic acid-protein complex partitioning taught by Gold et al. and Cathcart et al. by modifying the nucleic acid with photoreactive groups and irradiating nucleic acid-protein complexes to photocrosslink the complexes prior to partitioning to thereby obtain nucleic acid-protein complexes in their native conformation and obtain weak or transient nucleic acid-protein interactions as taught by Hanna (page 383, lines 7-10 and page 389, third full paragraph, lines 1-3) for the expected benefit of obtaining otherwise unobtainable complexes.

Regarding Claim 19, Gold et al. teach a method for the identification of a nucleic acid ligand from a candidate mixture of nucleic acids (Column 9, lines 14-40, Fig. 2 and Example 1), wherein said nucleic acid ligand binds a protein (Column 13, lines 1-6 and 15-20) the method comprising: contacting the candidate mixture with the protein wherein the nucleic acids having an increased affinity to the protein relative to the candidate mixture to form complexes (Column 36, Example 1, Column 36, lines 58-62); partitioning the increased affinity nucleic acids from the remainder of the candidate mixture (Column 13, lines 21-35 and Example 1, Column 36, lines 58-62); amplifying the increased affinity nucleic acids (Column 13, lines 39-47 and Example 1, Column 36, lines 63-68) to yields a ligand-enriched mixture of nucleic acids (Example 1, Column 37, lines 6-22), wherein a nucleic acid ligand is identified (Example 1, Column 37, lines 24-28). Gold et al. do not teach the method is automated wherein method steps are performed at one or more work stations on a work surface by a Cartesian robotic manipulator controlled by a computer. However, automated methods of identifying a nucleic acid from a mixture of nucleic acids were known in the art as taught by Cathcart et al. Specifically, Cathcart et al. teach the method for automated identification of a

nucleic acid binding partner from a mixture of nucleic acids using a Cartesian robotic means for contacting a nucleic acid binding partner within a mixture of nucleic acids (Fig. 1, #11, Column 13, lines 52-61 and Column 26, lines 20-38); a means for partitioning of nucleic acids having a high affinity for the nucleic acid binding partner using particle-bound affinity pairs (Fig. 1, #26 or 29 and Column 14, lines 9-68); and a thermocycling means for amplifying nucleic acids having high affinity for the nucleic acid binding partner (Fig. 1 #21 and Column 7, lines 19-34); and an identification means for identifying nucleic acid binding partner wherein the nucleic acids are labeled (Column 26, lines 20-23, Column 27, lines 64-68 and Column 28, lines 1-10). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply automated machine of Cathcart et al. wherein nucleic acid binding partners are identified to the closely related method of Gold et al. wherein nucleic acid ligands are identified because the skilled practitioner would have known that nucleic acid ligands and nucleic acid binding partners would have the same physical and chemical properties and because one skilled in the art would have known that automated methods produce consistent experimental results, precise manipulations and reduce hands-one operator time as taught by Cathcart et al. (Column 29, lines 50-55) therefore one skilled in the art would have been motivated to apply the automation of Cathcart et al. to the method of Gold et al. for the expected benefits of economy of time and labor. Gold et al. does not teach the nucleic acid contains a photoreactive group and irradiating the nucleic acid-target complex to thereby photocrosslink the nucleic acid-protein complex. However, modifying a nucleic acid with a photoreactive group and irradiating to thereby photocrosslink modified nucleic acid-protein complexes was well known in the art at the time the claimed invention was made as taught by Hanna. Specifically, Hanna teaches a method for identifying a nucleic acid that photocrosslinks to a protein comprising: contacting a candidate mixture of nucleic acids with a protein; irradiating to photocrosslink nucleic acid-protein complexes; partitioning the photocrosslinked nucleic acid-protein complexes (page 405, last paragraph-page 406, fifth full

paragraph, Isolation and Analysis); and identifying a nucleic acid photocrosslinked to the protein (page 408, last paragraph-through page 409). Additionally, Hanna teaches that modification of an RNA with photoreactive groups allows for the study of RNA-protein interactions in their native conformations (page 389, third full paragraph, lines 1-3) and that RNA-protein photocrosslinking traps weak or transient RNA-protein interactions which, if not photocrosslinked, might not survive isolation (page 383, lines 7-10). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify nucleic acid-protein complex partitioning taught by Gold et al. and Cathcart et al. by modifying the nucleic acid with photoreactive groups and irradiating nucleic acid-protein complexes to photocrosslink the complexes prior to partitioning to thereby obtain nucleic acid-protein complexes in their native conformation and obtain weak or transient nucleic acid-protein interactions as taught by Hanna (page 383, lines 7-10 and page 389, third full paragraph, lines 1-3) for the expected benefit of obtaining otherwise unobtainable complexes.

Response to Arguments

8. Applicant argues that while Gold et al teach the basic SELEX method, they do not teach automation of the process or photocrosslinking of nucleic acid ligands to their target and while Cathcart et al teach automated selection method, they do not teach aptamers or nucleic acid ligands or photocrosslinking, and therefore, the combination of Gold et al and Cathcart et al is insufficient to suggest the claimed automated SELEX method. Applicant further argues that Hanna does not cure the deficiencies of Gold et al and Cathcart et al because Hanna does not teach screening millions of synthetic oligonucleotides to identify nucleic acid ligands having the highest affinity to protein targets; Hanna makes no reference to SELEX-like process; and Hanna makes no suggestion regarding automation. Therefore, Applicant argues the combination of Gold et al, Cathcart et al and Hanna are insufficient to establish *prima facie* obviousness because there is no motivation to combine their teaching to obtain the claimed invention. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.

1992). In this case, Gold et al teach SELEX processes; Cathcart et al teach automation of known methods and motivation to automate known methods i.e. automated methods produce consistent experimental results, precise manipulations and reduce hands-one operator time as taught by Cathcart et al. (Column 29, lines 50-55); and Hanna teaches photocrosslinking and motivation to crosslink RNA-protein complexes i.e. crosslinking allows for the study of RNA-protein interactions in their native conformations (page 389, third full paragraph, lines 1-3) and that RNA-protein photocrosslinking traps weak or transient RNA-protein interactions which, if not photocrosslinked, might not survive isolation (page 383, lines 7-10). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify automated selection process taught by Gold et al. and Cathcart et al. by modifying the nucleic acid with photoreactive groups and irradiating nucleic acid-protein complexes to photocrosslink the complexes prior to partitioning to thereby obtain nucleic acid-protein complexes in their native conformation and obtain weak or transient nucleic acid-protein interactions as taught by Hanna (page 383, lines 7-10 and page 389, third full paragraph, lines 1-3) for the expected benefit of obtaining otherwise unobtainable complexes.

Applicant argues that the motivation provided by the examiner is not the necessary motivation because the purpose of the instant invention is to obtain aptamers with greater affinity not those with weak or non-specific binding. In response to applicant's argument that the instant invention is not drawn to obtaining weak or non-specific binding aptamers, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues that there is insufficient suggestion in Gold et al, Cathcart et al and Hanna to support a case of *prima facie* obviousness, but at most provide only general guidance and therefore only an invitation to experiment. The argument has been considered but is not found persuasive because Hanna clearly teach their photocrosslinking is useful for analyzing RNA-protein complexes and they teach motivation to photocrosslink such complexes i.e. modification of an RNA with photoreactive groups allows for the study of RNA-protein interactions in their native conformations (page 389, third full paragraph, lines 1-3) and that RNA-protein photocrosslinking traps weak or transient RNA-protein interactions which, if not photocrosslinked, might not survive isolation (page 383, lines 7-10). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the nucleic acids of Gold et al with photoreactive groups and irradiating nucleic acid-protein complexes to photocrosslink the complexes prior to partitioning to thereby obtain nucleic acid-protein complexes in their native conformation and obtain weak or transient

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nucleic acid-protein interactions as taught by Hanna (page 383, lines 7-10 and page 389, third full paragraph, lines 1-3) for the expected benefit of obtaining otherwise unobtainable complexes.

Applicant argues unexpected results have been obtained using the automated partitioning step of photoSELEX and cites co-pending Application 09/993,294 as evidence. However, Applicant has not illustrated how or why the results obtained in the '294 application are unexpected. Therefore, the argument is not found persuasive because it is not supported by evidence.

REQUIREMENT TO COMPLY WITH NUCLEIC ACID SEQUENCE RULES

9. The communication filed 26 February 2002 **is not fully responsive** to the Office communication mailed 15 August 2001 for the reason(s) set forth on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Since the above-mentioned reply appears to be *bona fide* attempt to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), applicant is given A PERIOD OF TIME CO-EXTENSIVE WITH THE TIME TO REPLY TO THE ABOVE OFFICE ACTION within which to correct the deficiency so as to comply with the sequence rules (37 CFR 1.821 - 1.825) in order to avoid ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

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10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

11. No Claim is allowed.
12. The examiner's Art Unit has changed from 1655 to 1634. Please address future correspondence to Art Unit 1634.
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
May 21, 2002



W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600